Int. J. Environ. Res. Public Health **2017**, *14*(5), 495; doi:10.3390/ijerph14050495

Article

Hospitalizations in Pediatric and Adult Patients for All Cancer Type in Italy: The EPIKIT Stu under the E.U. COHEIRS Project on Environment and Health †,‡

Prisco Piscitelli [1,*], Immacolata Marino [2], Andrea Falco [1], Matteo Rivezzi [1], Roberto Romano [3], Restituta Mazzella [3], Cosimo Neglia [3], Giul Della Rosa [3], Giuseppe Pellerano [3], Giuseppe Militerno [4], Adriana Bonifacino [5], Gaetano Rivezzi [6], Roberto Romizi [7], Giuseppe Miserotti Maurizio Montella [9], Fabrizio Bianchi [10], Alessandra Marinelli [11], Antonella De Donno [12], Giovanni De Filippis [13], Giuseppe Serravezza [1] Gianluca Di Tanna [14], Dennis Black [15], Valerio Gennaro [16], Mario Ascolese [17], Alessandro Distante [3], Ernesto Burgio [18], Massimo Crespi [19] Annamaria Colao [20]

[1] Medicina Futura Research, Southern Italy Hospital Institute (IOS), Centro Direzionale, Isola E3, Palazzo Avalon, 80143 Naples, Italy
[2] Department of Economics and Statistics and CSEF, University Federico II, 80131 Naples, Italy
[3] Euro Mediterranean Scientific Bio-Medical Institute, ISBEM, 72023 Mesagne (Brindisi), Italy
[4] Local Health Authority ASL Napoli 3 South, 80100 Naples, Italy
[5] St. Andrea Hospital, La Sapienza University, 00185 Rome, Italy
[6] Division of Neonatology, St. Anna & St. Sebastiano Hospital, 81100 Caserta, Italy
[7] Local Health Authority USL 8, 52100 Arezzo, Italy
[8] Local Health Authority USL Piacenza, 29121 Piacenza, Italy
[9] IRCCS G. Pascale Foundation, National Cancer Institute, 80131 Naples, Italy
[10] National Research Council, CNR-IFC, 56121 Pisa, Italy
[11] Department of Experimental Medicine, Second University of Naples (SUN), 80138 Naples, Italy
[12] Department of Biological and Environmental Sciences and Technologies (DISTEBA), University of Salento, 73100 Lecce, Italy
[13] Local Health Authority ASL LE, 73100 Lecce, Italy
[14] Centre of Primary Care and Public Health, Queen Mary University of London, London E14NS, UK
[15] Department of Epidemiology and Biostatistics, University of California San Francisco (UCSF), San Francisco, CA 94158, USA
[16] National Cancer Institute IRCCS San Martino, 16121 Genova, Italy
[17] Division of Pediatric Surgery, Salerno University Hospital "Ruggi D'Aragona", 84100 Salerno, Italy
[18] European Cancer and Environment Research Institute (ECERI), 21004 Bruxelles, Belgium
[19] Collegium Ramazzini, Bologna 40010, Italy
[20] Department of Clinical Medicine and Surgery, University Federico II, 80131 Naples, Italy

[*] Correspondence: Tel.: +39-081-7879-520; Fax +39-081-7879-481
† In memory of Prof. Massimo Crespi for his outstanding contribution to Epidemiology and Public Health throughout all his life.
‡ On behalf of the EPIKIT (Epidemiology of Cancer in Italy) Study Group under COHEIRS Project on Precautionary Principle (Europe for Citizens Program 2013–2014).
§ Deceased in September 2015.

Academic Editor: William Chi-shing Cho

Received: 15 December 2016 / Accepted: 15 April 2017 / Published: 9 May 2017

Abstract: *Background*: Cancer Registries (CRs) remain the gold standard for providing official epidemiological estimations. However, du CRs' partial population coverage, hospitalization records might represent a valuable tool to provide additional information on ca occurrence and expenditures at national/regional level for research purposes. The Epidemiology of Cancer in Italy (EPIKIT) study group been built up, within the framework of the Civic Observers for Health and Environment: Initiative of Responsibility and Sustainab (COHEIRS) project under the auspices of the Europe for Citizens Program, to assess population health indicators. *Objective*: To assess the bu of all cancers in Italian children and adults. *Methods*: We analyzed National Hospitalization Records from 2001 to 2011. Based on social secu numbers (anonymously treated), we have excluded from our analyses all re-hospitalizations of the same patients (n = 1,878,109) over the e 11-year period in order to minimize the overlap between prevalent and incident cancer cases. To be more conservative, only data concerning last five years (2007–2011) have been taken into account for final analyses. The absolute number of hospitalizations and standard hospitalization rates (SHR) were computed for each Italian province by sex and age-groups (0–19 and 20–49). *Results*: The EPIKIT data included a total of 4,113,169 first hospital admissions due to main diagnoses of all tumors. The annual average number of hospital admiss due to cancer in Italy has been computed in 2362 and 43,141 hospitalizations in pediatric patients (0–19 years old) and adults (20–49 years respectively. Women accounted for the majority of cancer cases in adults aged 20–49. As expected, the big city of Rome presented the hig

represents a crucial piece of information for planning adequate healthcare services and assessing social alarm phenomena. Our findings cal specific risk assessment programs at local level (involving CRs) to search for causal relations with environmental exposures.

Keywords: hospitalizations; cancer incidence; children; pediatric cancer; adult cancer; environment and health

1. Introduction

Until 1955, the word "tumor" was generically defined as "an occupational disease of chemical industry workers" in the most pres encyclopedic dictionaries [1]. Nowadays, cancer is generally associated with old age, and its continuous increase—observed throughout th century in all industrialized countries—is generally explained as a consequence of progressive accumulation of oxidative, stochastic (ra genetic damage, along with ongoing improvement in our diagnostic capacities. From the end of the 1980s to date, cancer has involved individ all ages, including younger people, whose number it is difficult to estimate [2]. Cancer incidence data are essential for epidemiological purpo well as for planning screening campaigns and cancer primary prevention or surveillance. The implementation of Cancer Registries (CRs) rep the gold standard methodology for data collection and cancer surveillance at the local level [3].

In Italy, a network of population-based local cancer registries has been established (Italian Association of Cancer Registries, AIRTUM) in o set high qualitative standards in data collection that result in reliable reports, with data available on the AIRTUM website. However, the AI CRs does not cover the entire Italian population, with a remarkable difference in CRs population coverage among Northern (50.2%), Central (and Southern areas of the Country (17.9%) [4]. In the last decade, cancer incidence estimation at national level have been provided in the fra specific cooperation between the National Institute of Public Health (ISS), the National Cancer Institute of Milan, and the AIRTUM. They adopted the Mortality-Incidence Analysis MODel (MIAMOD) statistical model, which represents a back-calculation approach to estim morbidity of chronic irreversible diseases from existing mortality and survival data [5,6].

Referring only to CRs when searching for epidemiological data about the overall and cancer-specific burden of tumors in general populatio well-defined subgroups (i.e., pediatric population or younger adults) might represent a limitation, due to the problem of CRs' partial pop coverage [7]. Despite possible limitations related to underestimation produced by the proportion of cancer patients that is not hospit additional secondary databases such as hospital discharge records (HDR) have been proposed by researchers as potential tools to improve the of assessing the burden of several diseases, including cancer [8,9,10,11,12]. The accuracy of these secondary data sources has been spec explored [13,14]. A study carried out by Penberthy et al. used both CRs and HDR for the detection of incident cancer cases [15]. In our pr studies, we have used HDR as secondary data source to specifically address the issue of breast cancer [12,16].

In this paper, we present the first analyses performed on the national hospital discharge records maintained at central level by the Mini Health concerning hospitalization due to main diagnosis of overall cancer, as a result of the work carried out by the Epidemiology of Cancer i (EPIKIT) study group. This latter initiative has been promoted within the framework of the European Civic Observers for Health and Enviro Initiative of Responsibility and Sustainability (COHEIRS) project under the auspices of the European Union's "Europe for Citizens" Progra COHEIRS—coordinated by ALDA, the European Association of Local Democracy Agencies at the European Council in Strasbourg was imple in Italy by the Euro Mediterranean Scientific Bio-Medical Institute (ISBEM) and International Society Doctors for the Environment (ISDE) an been acknowledged as one of the three best European projects of the year 2013. The aim of the COHEIRS project was to foster the implementa the "precautionary principle" (with specific focus on health and environment assessment) stated in the Maastricht Treaty and at Article 191 European Union Treaty [17]. Precautionary principle should be invoked when scientific final proofs of toxicity for the environment or hea lacking, but some evidence lead to possible concerns.

Although CRs remain the gold standard methodology to collect epidemiological information on cancer incidence at local level, we attem estimate the burden of cancer at regional and province level for the entire nation thanks to the specific expertise developed by our study gr the treatment and analysis of HDR. These analyses could also be useful in better understanding the consistency of social alarm that have sp certain areas of the country (i.e., the Campania region) concerning possible environmental threats to human health related to illegal ac leading to soil/air/water pollution. Our work could help in explaining the widespread perception of higher incidence of tumors in pe population (0–19 years old) and adults belonging to those age groups (20–49 years old) generally excluded by official screening for prevention. At the same time, our work could be used by decision makers in planning healthcare services to be offered at local level in the oncology.

2. Materials and Methods

2.1. Database

Information concerning hospitalizations occurring in Italian hospitals are registered in Hospital Discharge Records (HDRs), which are colle the Italian Ministry of Health's national hospitalization database. The information is anonymous and includes the region and hospital wh patients have been hospitalized, type of hospitalization (ordinary admission or day hospital), region and province where the patient com local health authority (ASL) who is paying for the hospitalization costs, patient's age, gender, main diagnosis, secondary diagnoses (comor which are not the cause of the hospitalization), procedures performed, diagnosis related group (DRG) and length of the hospitalization. HD kept at the central level by the Ministry of Health since the year 1999, but the national hospitalization database has been fully implemented Italian regions only since 2001. It is important to point out that, in the national hospitalization database, people admitted at hospitals loc different region or provinces (different from those ones where patients live), are classified according to their hometown address. Therefore was no possibility of misclassification of patients from one province in another. However, it was impossible to assess the time people hav living in a specific region or province.

The Italian Ministry of Health has officially provided ISDE Campania (who is part of the COHEIRS Project and promoted the EPIKIT study with the full database covering all hospitalizations occurred in Italy between 2001 and 2011 due to cancer diagnoses. The quality of these known to be very high and certified at the central level by the Ministry of Health, with completeness and reliability of records (in te correspondence between hospitalizations and individual social security numbers as well as in terms of absence of errors or missing data) v from 95.6% (year 2001) and 99.8% (from year 2008), respectively, as reported in our previous studies [9,17].

Our dataset included all hospitalized patients identified based on the following International Classification of Diseases (ICD-9-CM)

(bladder cancer), 185 (prostatic cancer), 180 (uterine cervix cancer), 182 (uterine cancer), 183 (ovary cancer), 153 (colon cancer), 157 (pan cancer), 186.0 and 186.9 (testicular cancer), 189 (kidney and urinary tract cancer), 155 (liver cancer), 200.0–200.2, 201.0–201.9, 202.0, 203.0 203.8, 204.0, 204.2, 204.8, 204.9, 205.0, 205.1–205.3, 205.8, 205.9, 206.0–206.3, 206.8–206.9, 207, 208 (malignant tumors of lymphatic and hemo system), 1510–1519 (gastric cancer), 1501–1509 (esophageal cancer), 1580–1589 (peritoneal cancer), 1560–1569 (gall-bladder and biliary tract c We considered both ordinary hospitalization and day hospital regimens.

Based on social security numbers (which were treated anonymously), the Ministry of Health has enabled us to exclude all hospital re-adm of the same patient over the entire study period, in order to minimize possible bias related to the overlapping between prevalent and incident cases. To exclude hospital re-admissions from our analysis, we have considered as hospitalization "index" only the first hospital admission o entire study period (2001–2011). Patients presenting the same social security number (treated anonymously) and the same major diagnosi considered as the same person, and they were computed only one time. This kind of approach to minimize the overlapping between prevale incident cases has been already used and validated by the Environmental Protection Agency of Piemonte Region for the assessment of popu health indicators [18]. After having identified first hospital admissions for the cancer diagnosis that occurred between 2001 and 2011, we re relapses and admissions for previous cancer patients from hospitalizations taking place during the entire 11-year period. To be more conse and exclude prevalent cancer cases and disease relapses, we have included in our final analyses only the last five years (2007–2011).

2.2. Analyses Performed and Data Treatment

The total number of records contained in the official database provided by the Ministry of Health were 5,991,278. About 24,194 record missing information concerning the province where the hospitalized patient was living. We have excluded from our analyses all re-hospitali concerning the same patient (n = 1,878,109) over the entire 11-year period. As a result, the Epikit Database contains a total of 4,113,169 "first h admissions" due to main diagnoses of any cancer detailed in the previous paragraph. The absolute frequencies (number of hospitalizations computed for each Italian region (R) and province (P), by sex (S), year (y), and 10-year age groups (x):

$$n^{S}_{y,x}\,(\mathrm{Reg\ or\ Prov}) \tag{1}$$

The standardized hospitalization rate (H) per 100,000 inhabitants was computed by referring to the Italian population as standard $Pop^{S}_{y,x}$ (year 2001 (y) per age group (x) and sex (S):

$${}^{S}_{R}H_{y,x} = \frac{[\Sigma_{x}\,{}^{S}_{R}h_{y,x}] * [Pop^{S}_{y,x}(IT)]}{[\Sigma_{x}\,P^{S}_{y,x}(IT)]} \times 100 \tag{2}$$

$${}^{S}_{P}H_{y,x} = \frac{[\Sigma_{x}\,{}^{S}_{P}h_{y,x}] * [Pop^{S}_{y,x}(IT)]}{[\Sigma_{x}\,P^{S}_{y,x}(IT)]} \times 100 \tag{3}$$

Data were analyzed and processed using Stata (StataCorp, College Station, TX, USA) and Excel (Microsoft, Redmond, WA, USA) softwar and sex standardized rates per region and province were calculated based on population data provided by the Italian National Institute for St (ISTAT). The results of the analyses in this first paper have been studied as cumulative data (all tumors) per each Italian region and pr according to sex and age groups (0–19; 20–49). Data are specifically presented per province (in tables and on maps) as absolute num hospitalizations and standardized hospitalization rates for each of the years from 2007 to 2011.

3. Results

Table 1 and Figure 1 report the annual average standardized hospitalization rate (SHR) per region due to all cancers in people aged 0–10 old. Table 2 and Table 3 present the overall number of new hospitalizations and the corresponding standardized hospitalization rates per 1 inhabitants per province due to all cancers in pediatric population aged 0–19 and adults aged 20–49 years old, respectively.

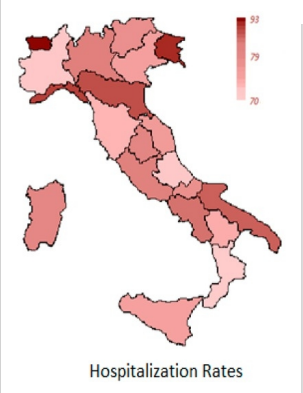

Figure 1. Overall regional cancer standardized hospitalization rates (SHR) per 100,000 in the population aged 0–100 years old (average annual value).

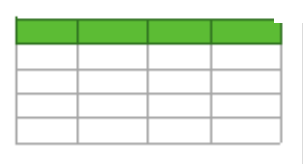

Table 1. Overall cancer standardized hospitalization rate per region in population aged 0–100 years old (Average Annual Value).

number of new hospitalizations due to cancer per region and province from 2007 to 2011. Pediatric patients aged 0–19 years old.

Table 3. Standardized hospitalization rate (SHR) per 100,000 and overall number of new hospitalizations due to cancer per region and province from 2007 to 2011. Adults aged 20–49 years old.

The average annual number of hospitalizations due to all cancers in Italy was 2362 in pediatric populations (0–19 years old) and 43,141 in aged 20–49 years old. Women accounted for the majority of cancer cases in young adults 20–49 (data not presented). As expected, in te absolute number of hospitalizations, the biggest cities of Rome, Naples, and Milan display the highest values in both the examined age g followed by smaller cities (number of pediatric hospitalizations > 100) such as Turin, Bari, Salerno, Caserta, Catania and Palermo. All these were always at the top ten places in both the examined age groups, Particularly, Rome presented the highest average annual number of pe cancers (n = 392, SHR = 9.9), followed by Naples (n = 378; SHR = 9.9) and Milan (n = 212; SHR = 7.3). Rome displayed also the highest num average annual hospitalizations due to cancer in young adults aged 20–49 years old (n = 3633; SHR = 89.0), followed by Milan (n = 2491; SHR = Naples (n = 2398; SHR = 74.8), Turin (n = 1376; SHR = 63.6), and minor cities such as Bari (n = 1103; SHR = 85.8), Catania (n = 924; SHR = 83.2), (n = 906; SHR = 71.1), Salerno (n = 781; SHR = 69.3), Bologna (n = 735; SHR = 77.5), Caserta (n = 673; SHR = 69.4), Lecce (n = 645; SHR = 81.1), Be (n = 645; SHR = 57.5), Florence (n = 635; SHR = 68.8), Padova (n = 629; SHR = 66.9), Verona (n = 617; SHR = 67.2), Genova (n = 614; SHR = 80.0).

When looking only at SHR of pediatric cancers, minor cities (i.e. Imperia, Isernia and others) presented values >10 per 100,000, with only 2 per year. Despite huge differences in the number of hospitalizations, when looking at the SHR in pediatric patients, the highest values (100,000) were recorded in provinces belonging to well defined areas: Isernia, Naples, Caserta, Salerno, Avellino (region Molise and Cam Rome, Frosinone, Rieti, Latina, Viterbo and Terni (Region Lazio and Umbria); Bari, Foggia, Barletta/Andria and Brindisi (Puglia); L'Aquila, T Chieti, Ascoli Piceno (Abruzzo and Marche); Parma (Emilia Romagna); Aosta (Val d'Aosta Region); Vercelli, and Imperia (Piemonte and Li Cagliari, Oristano, Ogliastra, Medio Campidano (Sardinia); Catania, Messina, Trapani, Enna, Caltanissetta (Sicily).

Similarly, also when looking at the SHR in adult patients aged 20–49 years old, the highest values (≥75 per 100,000) were displayed in the Sardinia island, Liguria and Marche Region, and in the following Provinces: Milan, Alessandria, Udine, Gorizia, Ravenna, Ferrara, Rimini, Pia Rovigo, Bologna and Parma (in Northern Italy); Rome, Frosinone, Rieti, Latina, L'Aquila, Lucca, Livorno, Massa-Carrara, Perugia and Terni (Italy); Messina, Enna, Caltanissetta, Catania, Campobasso, Bari and Lecce (in Southern Italy).

Women always presented SHR values higher than men (data not presented). Figure 2 and Figure 3 show on a map the average annual v standardized hospitalization rate (SHR) per 100,000 inhabitants per province in pediatric population aged 0–19 and in young adults 20–49 du cancers.

Figure 2. Standardized Hospitalization Rate (SHR) per 100,000 per each Italian province due to main diagnosis of cancer diagnosis of (all tumors) in pediatric population (0–19 years old).

Figure 3. Standardized Hospitalization Rate (SHR) per 100,000 inhabitants per each Italian province due to main diagnosis of cancer (all tumors) in adults aged 20–49 years old.

4. Discussion

Our objective was to provide a preliminary tabulation of hospitalizations occurred in Italy from 2007 to 2011. The specific goal of our study look at the hospitalizations due to all cancers in the Italian provinces, with specific focus on youngest age groups, namely pediatric populati adults ≤50 years old, which are not covered by screening campaigns. The aim was to provide some data about the hospital admissions of patients including those areas where cancer registries (CRs) have not been activated or provide only a partial population coverage. Actually than 50% of the Italian population is not covered by CRs and therefore no data are available on cancer incidence rates concerning all the r especially for Southern Italy.

Since the potential and limitations of CRs and HDR have already been addressed [8,9,10,11,12,13,14,15,16], this work might provide a first general picture about the burden of cancer in Italy concerning younger people, based on real official national data such as hospitalization r We were not still able to split the database for many age groups (the analyses by smaller age groups will be presented in future publication decision to focus on pediatric population (0–19 years old) and young adults (20–49 years old) is closely related to the need of providing infor about the possible impact of environmental threats to human health coming from the carcinogen substances officially classified by

investigated in many big cities across Europe, including Rome [20,21,22]. However, it was not the aim of this study to specifically look at relations between tumors and environmental or personal exposures.

Recent reports of a significant increase in childhood cancer in Europe [2] and especially Italy [23] has caused concern, pushing some auth critically reconsider this dominant model of carcinogenesis [24] and to reconsider quality, comparability and methods of analysis of d childhood cancer [25]. Cancer has become the leading cause of death among children over the first year of age. Even after adjusting for popu growth and improved detection of certain types of cancer, we have observed an increased in childhood cancer over the past 40 years. A increase in cancer cases has been specifically documented in the first year of age, suggesting that the cancers may originate from maternal an exposure to pro-carcinogenic agents, or have an epigenetic or gametic origin [2,26]. These data suggest that exposure to carcinogens from po could play a bigger role in causing children cancer than that played by unhealthy personal habits in adults (i.e., cigarette smoking)".

Looking only at "rates" might be restrictive when assessing the global burden of cancer diseases and the perception by population. examining cancer rates in the Campania Region, a big city such as Naples with about 300 new cases per year could show a SHR similar to th smaller towns with 10–20 new cases per year. For example, the SHR in the large city of Naples was 8.89 in year 2011, which is smaller than th of the smaller town of Isernia with an SHR of 10.43. However, on an absolute scale, more than 300 cases of pediatric cancer would arise in Na a single year, which is much higher than 8 pediatric cases per year hospitalized in Isernia. This perceived difference in the number of cancer c the population of Naples could contribute to public alarm and panic. Similarly, the overall 280 hospitalizations due to pediatric cancer in (SHR 2011: 5.37) are not considered as a particular problem compared to the 20 cases of Teramo (SHR 2011: 5.73) when looking only at "rate should also look at the problem from an ethical point of view: if we consider as "normal" that cities with a higher number of children mus more incident cancer cases, it could be questioned if we can accept in our society that "more children means more tumors".

It is interesting to point out that public perception acts in a completely different way (no social alarm) in other areas presenting even more re number of pediatric hospitalizations, such as Rome and surroundings (more than 300 new cases per year on average only in the capital city would probably suggests that information provided to the population (i.e., the discovery of a huge number of illegal deposits or dumping incineration of dangerous wastes) contribute to create panic and social alarm. Beyond the social consequences of having more children or suffering from cancer, we believe it is important for decision makers to have information about the absolute number of cancer cases in or provide adequate both in-the hospital and in-home-based healthcare facilities to take care of a huge number of patients.

In this paper, we have presented our data per province and for all cancer types. Of course, we are aware that the highest observed hospitali rates could reflect problems that are specifically attributable to the biggest cities or to single towns within the province (with the rest of the ar being responsible for the increased rates). In addition, particularly high values of SHR observed in smaller provinces might be the consequ the higher incidence of specific tumors related to particular (environmental or professional) exposures typical of that territory. Of course, onl CRs are able to accomplish this level of characterization. This is the case of Taranto, where the local cancer registry has recorded higher inc rates of pediatric tumors than those found out in our analyses [27]. Particular attention should be paid to the higher incidence of cancer in (mostly women) in the entire Sardinia Island, where the activity of CRs is still at the initial stages.

We believe that cancer hospitalization data per province presented in this study may provide a first interesting rough picture of the problem, that can be further and deeper investigated through the use of local CRs (where and when available). We are also aware that the hospitalization records for epidemiological purposes present a series of limitations mainly consisting in the unavoidable "false negative cancer patients who are not hospitalized because treated at ambulatorial level and consequently not included in the national hospitali database. Despite hospitalization records have not been conceived as a primary epidemiological instrument but as an administrative tool, th completed only after histological exam has allowed a final diagnosis. Therefore, the use of hospitalization records for epidemiological purp particularly valuable. Of course, there is the possibility of an under-estimation produced in our study by the presence of cancer patie hospitalized, which can be detected only by CRs as gold standard methodology. However, the aim of this study was to provide a first picture phenomenon at national level, including also those areas not covered by CRs, which could provide detailed data once activated.

It is interesting to point out that our findings about the incidence of all pediatric cancer in Italy (with about 11,800 new cases per year over a period) are consistent with AIRTUM projections for years 2016–2020 which estimate about 11,000 new cases of cancer in the age group 0–19 National Association of Cancer Registries 2013 Report [28].

Data presented in this paper might represent an initial step which should encourage scientists and public bodies to assess the causes increasing cancer hospitalization rates in different Italian areas, with the ending of the traditional gap between Northern and Southern Italy field of cancer diseases. The role played by environmental pollutants [29], food and water contamination (i.e., pesticides use, toxic wastes, metals, dioxins and others), nutritional, professional and other personal habits should be investigated. Finally, the higher SHR rates displayed study in young women (compared to men) aged 20–49 years old should be considered as a very interesting finding, as it is only partially likel the effect of population screening campaigns. Actually, mammographic screening campaigns involve older females aged >50 years old and on for the prevention of uterine cervix cancer are performed at younger age. Therefore, this latter finding could probably reflect a higher incid some specific female tumors (i.e., breast and thyroid cancer) as suggested by AIRTUM Reports in the younger age groups [28,30,31].

5. Conclusions

Despite the limitations due to the possible underestimation of cancer incidence, it is feasible and potentially useful to use hospitalization r as secondary data source where cancer registries do not cover an entire province or region, in order to provide preliminary information of burden. As expected, the biggest Italian cities showed the highest number of hospitalizations, with well-defined areas being characterized by pronounced SHR. In addition to the SHR, the absolute number of new cancer cases represents a crucial information for a global assessment problem (including healthcare, social, environmental and other evaluations) as well as for adequate planning of healthcare services by d makers at regional level. Our results over a 5-year period are consistent with AIRTUM projections for years 2016–2020 and call for speci assessment programs at local level to search for causal relations with environmental and personal or professionals exposures, that should perf on cancer registries data and case-control studies as the most qualified tool for that.

Acknowledgments

This paper is a result of institutional research activities of Medicina Futura Research (IOS/Coleman Ltd., Naples, Italy) in cooperation w Euro Mediterranean Scientific Biomedical Institute (ISBEM, Brindisi, Italy) and the International Society Doctors for the Environment (ISDE

The COHEIRS Project is coordinated at European Level by the Association of Local Democracy Agency (ALDA) in Strasbourg and it is impler in Italy by ISBEM and ISDE. Authors are grateful to the ALDA General Director Antonella Valmorbida and to ALDA staff, especially to Boaria, Anna Ditta and Aldo Xhani for their support in carrying out COHEIRS project, as well as to Donato Cafagna (Delegate of Italian Gover for environmental affairs in Campania).

Author Contributions

All authors provided substantial contribution to the production, analysis and interpretation of the results. Prisco Piscitelli, Immacolata M Andrea Falco, Matteo Rivezzi, Roberto Romano, Restituta Mazzella, Cosimo Neglia, Giulia Della Rosa, Giuseppe Pellerano, Giuseppe Mil Adriana Bonifacino, Gaetano Rivezzi, Roberto Romizi, Giuseppe Miserotti, Maurizio Montella, Fabrizio Bianchi, Alessandra Marinelli, Anton Donno, Giovanni De Filippis, Giuseppe Serravezza, Gianluca Di Tanna, Dennis Black, Valerio Gennaro, Mario Ascolese, Alessandro Di Ernesto Burgio, Massimo Crespi, Annamaria Colao have conceived the study together and contributed to write and prepare the manuscript the final approval and submission. Prisco Piscitelli, Immacolata Marino, Andrea Falco, Roberto Romano, Restituta Mazzella, Cosimo Neglia, Della Rosa, Giuseppe Militerno, Gianluca Di Tanna, Valerio Gennaro, Massimo Crespi performed the statistical analyses.

Conflicts of Interest

The authors declare no conflict of interest.

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